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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/963,288	11/03/97	NORSTEDT G	10806-48

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EXAMINER	
BAKER, A	
ART UNIT	**PAPER NUMBER**
1632	19

DATE MAILED: 11/22/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

File Copy

Office Action Summary

Application No.	Applicant(s)
08/963,288	Norstedt et al.
Examiner	**Group Art Unit**
Anne-Marie Baker, Ph.D.	1632

☒ Responsive to communication(s) filed on *Aug 31, 2000* .

☒ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1, 2, 5, 7-11, 15-17, 19-21, 23-32, 34-36, 39-42, and 44-54* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1, 2, 5, 7-11, 15-17, 19-21, 23-32, 34-36, 39-42, and 44-54* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☒ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☒ received in Application No. (Series Code/Serial Number) *08/809,256* .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

The amendment filed August 31, 2000 (Paper No. 18) has been entered. Claims 1, 2, 5, 8, 10, 19, 23, 25, 27, 28, 30, 31, 32, 34, 41, 44, and 46-48 have been amended. Claims 22, 33, and 43 have been cancelled. Claims 49-54 have been newly added.

Claims 1, 2, 5, 7-11, 15-17, 19-21, 23-32, 34-36, 39-42, and 44-54 are pending in the instant application.

The following rejections are reiterated or newly applied and constitute the complete set of rejections being applied to the instant application. Rejections and objections not reiterated from the previous Office Action are hereby withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 19-21, 39, 40, and 44-52 stand and are rejected under 35 U.S.C. 112, first paragraph, for reasons of record as advanced in the previous Office Action mailed 4/26/00 (Paper No. 16), as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 1, 2, 19-21, 39, 40, and 46-52 are directed to an *in vitro* method of enhancing the transcription of a gene.

Applicants submit that Claim 1 and Claims 19 and 46 have been amended to delete the limitations of "providing upstream of said promoter six copies of an enhancer element" and "providing upstream of the promoter at least one enhancer element", respectively, and to include the limitations "transfecting the eukaryotic host cell with six copies of an enhancer element" and "transfecting the eukaryotic host cell with at least one enhancer element", respectively. However, the amendment to the claim does not overcome the instant ground of rejection. To work, the enhancer element must be incorporated into the genome upstream of the promoter of the DNA construct recited in the claim. Gene targeting would be required to accomplish this. For example, Claim 19 involves first placing the DNA construct in the host cell, then transfecting the host cell with the enhancer element. The enhancer element cannot be incorporated randomly into the genome of the host cell. The arrangement of genetic elements (i.e., the enhancer, promoter, and structural gene) is critical to the operability of the invention. Thus, the amendment to the claims does not overcome the rejection.

Applicants argue that Examples 2, 4, and 5 describe the transfection of host cells and further describe placing the DNA construct in an environment wherein transcription can occur, such as a cell. Applicants conclude that the claims are supported by an enabling disclosure. However, a description of transfection of host cells is not sufficient to enable the claims, as the arrangement of genetic elements is critical to the operability of the invention, and the claimed method would not work as the method steps do not involve gene targeting, and consequently the enhancer element is randomly integrated into the genome of the host cell, nowhere near the DNA construct recited in the claim.

Claims 44 and 45 are directed to an isolated DNA construct comprising a promoter and six repeats of an enhancer consisting essentially of the sequence TTCTGAGAA.

Applicants argue that Example 2 demonstrates that a DNA construct comprising a promoter and six repeats of an enhancer may be used to prepare an expression plasmid containing a recombinant hormone responsive reporter consisting of six repeats of an enhancer element and a promoter. However, the construct described in the example includes a reporter gene. The rejection states that the specification fails to provide an enabling disclosure for the claimed DNA constructs because the specification does not teach how to use a DNA construct that does not comprise any gene. In the absence of specific guidance, one skilled in the art would not know how to use a DNA construct comprising only multiple copies of an enhancer element and a promoter. Thus, the skilled artisan would have been required to engage in undue experimentation to use the claimed DNA constructs. Applicants further argue that Claim 54 recites an isolated DNA construct in accordance with Claim 44, further comprising a structural gene. This does not obviate the rejection of Claims 44 and 45.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 2, 5, 7-11, 15-17, 19-21, 23-26, 34-36, 39-42, and 44-54 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 2, 19-21, 39-42, and 46-52 are indefinite because the arrangement of the genetic elements (i.e., the enhancer, promoter, and structural gene) are not specified. As discussed above, the arrangement of the genetic elements is critical to the operability of the invention. The claims have been amended to recite "transfecting the eukaryotic host cell with six copies of an enhancer element" instead of "providing upstream

of said promoter six copies of an enhancer element." Thus, prior to amendment, the claims did specify the arrangement of genetic elements.

Claims 1, 2, 39, 40, and 51 are indefinite in their recitation of "transfecting the eukaryotic host cell with six copies of an enhancer element" because it is unclear whether only six copies of the element are used to perform the transfection or six copies of the element actually go into the cell and are incorporated into the genome of the cell. The number of copies of the enhancer element incorporated into the genome of the cell as a result of the transfection is not specified.

Claims 5, 7-11, 15-17, 23-26, 34-36, 44, 45, 50, 53, and 54 are indefinite in their recitation of "wherein the enhancer element consists essentially of the nucleotide sequence TTCTGAGAA, with the proviso that the nucleotide sequence is not the nucleotide sequence SEQ ID NO: 1" (or equivalent claim language) because it is unclear how "consists essentially of the nucleotide sequence TTCTGAGAA" could be construed to encompass the 52 nucleotide sequence of SEQ ID NO: 1. The inclusion of the proviso in combination with "consists essentially of" language raises the question of the intended scope of the phrase "consists essentially of" as used in this claim. The metes and bounds of the enhancer element recited in the claims are not clearly set forth.

Claims 10 and 17 are indefinite in their recitation of "said enhancer element comprises at least one copy of the nucleotide sequence SEQ ID NO: 1" as "said enhancer element" cannot comprise "at least one copy of the nucleotide sequence SEQ ID NO: 1" because Claim 8, from which Claims 10 and 17 depend, already carries the proviso that the nucleotide sequence is not the nucleotide sequence of SEQ ID NO: 1.

Claims 19-21 and 49 are indefinite in their recitation of "transfecting the eukaryotic host cell with at least one enhancer element" because it is unclear if only "at least one" enhancer element is used to perform the transfection or if only "at least one" enhancer element actually goes into the cell and is incorporated into

the genome of the cell. The number of copies of the enhancer element incorporated into the genome of the cell as a result of the transfection is not specified.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 19, 20, 49, and 54 stand and are rejected under 35 U.S.C. 102(b) as being anticipated by Yoon et al. (1990) for reasons of record advanced in the previous Office Action mailed 4/26/00 (Paper No. 16).

As amended, the claims are directed to an *in vitro* method of enhancing the transcription of a gene in a DNA construct comprising a structural gene for a desired protein or polypeptide and a promoter upstream of the structural gene, wherein the method comprises transfecting a eukaryotic host cell with at least one enhancer element consisting of the nucleotide sequence TTC TGA GAA, and exposing the DNA construct to a hormone.

Applicants argue that there is no teaching in Yoon et al. of a segment smaller than the 50 bp segment set forth as SPI-GHRE which is responsive to growth hormone. Applicants further argue that there is no teaching of an enhancer element consisting of the nucleotide sequence TTCTGAGAA. However, the claims continue to read on the method disclosed by Yoon et al. because the constructs described by Yoon et al. include the nucleotide sequence TTCTGAGAA and the instant claim recites transfecting a host cell with at least one enhancer element consisting of the nucleotide sequence TTCTGAGAA. As discussed above, the

skilled artisan would not expect a piece of DNA consisting of only these 9 nucleotides to incorporate upstream of the promoter recited in the claim. However, once incorporated into the proper location, some spacing between the promoter and the enhancer element is to be expected. The constructs described by Yoon et al. are of this type (i.e., the enhancer element is not directly adjacent to the promoter, rather there are a number of nucleotides that act as spacers between the enhancer and the promoter). Yoon et al. need not teach a segment smaller than the 50 bp segment set forth as SPI-GHRE which is responsive to growth hormone, because the segment that they used included the nucleotide sequence recited in the claim and the arrangement of genetic elements (i.e., enhancer, promoter, structural gene) is the same as that described in the instant specification. The enhancer element that Yoon et al. used did in fact "consist of" TTCTGAGAA despite the fact that they included some flanking sequences in their constructs as well. It is not necessary that Yoon et al. recognize or teach the minimal sequence that will function as an enhancer, because no matter how long the piece of DNA is initially, once it is incorporated into the DNA construct it necessarily becomes flanked by other nucleotides.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 27-32 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Lindquester et al. (1989) for reasons of record advanced in the previous Office Action mailed 4/26/00 (Paper No. 16).

The claims are directed to an expression vector comprising at least one enhancer element consisting essentially of the nucleotide sequence TTCTGAGAA, an isolated eukaryotic host cell containing the expression vector, and a DNA construct comprising a promoter, a structural gene and at least one enhancer element comprising the sequence TTCTGAGAA.

Applicants arguments have overcome the rejection as directed to the enhancer element.

Applicants argue that Lindquester et al. provides no motivation for making an expression vector comprising the tropomyosin gene. However, the stated motivation for making an expression vector comprising the tropomyosin gene was to produce the protein in culture. One of skill in the art would have anticipated a reasonable expectation of success for making the expression vector and host cell comprising the expression vector because only standard molecular biology techniques are required to make such compositions. Therefore, it would have been obvious to one of skill in the art at the time of the invention to have made an expression vector and a host cell comprising the expression vector, wherein the expression vector comprises an enhancer element including the nucleotide sequence TTCTGAGAA. As stated previously, one of skill in the art would have been motivated to use the nucleotide sequence disclosed by Lindquester et al. to construct an expression vector and a host cell comprising the expression vector in order to produce tropomyosin in culture for further study of the protein and the regulatory sequences driving expression of the protein. The vector would have necessarily contained the enhancer element present in the gene. Furthermore, the hormone responsiveness of the element is an inherent property of the element. Thus, even if the hormone responsiveness of the genetic element was not recognized, the presence of the DNA sequence would confer hormone responsiveness to the disclosed gene. Applicants assert that Claims 27-32 are not obvious over Lindquester et al., but Applicants have not offered any reasons as to why the expression

vector and host cell are not obvious. Applicants arguments are directed to the enhancer element and its function.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Baker whose telephone number is (703) 306-9155. The examiner can normally be reached Monday through Thursday and alternate Fridays from 9:00 AM to 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen Hauda, can be reached on (703) 305-6608. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-8724.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

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